ACUTE TOXICITY SUMMARY

METHYL BROMIDE

(bromomethane; monobromomethane)

CAS Registry Number: 74-83-9

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**3,900 µg/m**
Critical effect(s)	serious CNS effects: labored breathing, prostration, decreased activity, tremors, lacrimation
Hazard Index target(s)	Nervous System; Respiratory System; Reproductive/developmental

II. Physical and Chemical Properties (HSDB, 1994)

Description	colorless gas
Molecular formula	CH_3Br
Molecular weight	94.95
Density	3.88 g/L @ 25°C
Boiling point	3.6°C
Melting point	-93.7°C
Vapor pressure	1,420 mm Hg @ 20°C
Flashpoint	unknown
Explosive limits	unknown
Solubility	soluble in ethanol, benzene, carbon disulfide, and 1.75% (w/w) in water
Odor threshold	20.6 ppm
Odor description	sweetish odor
Metabolites	methanol, bromide, 5-methylcysteine
Conversion factor	1 ppm = 3.89 mg/m^3 @ 25°C

III. Major Uses or Sources

Methyl bromide (MeBr), introduced in the U.S. from Europe in the 1920s, was used historically as an industrial fire extinguishing agent. Current uses of MeBr include the fumigation of homes and other structures for termites and other pests. Methyl bromide is also used to fumigate soil before planting, and fruits and vegetables after harvest. In 1981, 6.3 million pounds of MeBr were reported to have been used in California (Alexeeff and Kilgore, 1983). In 1991, its use had grown to 18.7 million pounds in the state (Cal/EPA, 1993).

IV. Acute Toxicity to Humans

Symptoms (in approximate increasing severity) following acute exposure to MeBr include: 1. dizziness and headache; 2. anorexia, nausea, vomiting, and abdominal pain; 3. lassitude, profound weakness, slurring of speech, and staggering gait; 4. transient blurring of vision, diplopia, and even temporary blindness; 5. mental confusion, mania, tremors, and epileptiform convulsions; 6. rapid respiration, associated with signs of severe pulmonary edema, cyanosis, pallor, and collapse; 7. coma, areflexia, and death from respiratory and circulatory collapse (HSDB, 1994).

Low-level subchronic vapor exposures have produced a syndrome of persistent numbness in the hands and legs, impaired superficial sensation, muscle weakness, unsteadiness of gait, and absent or hypoactive distal tendon reflexes. Late sequelae include bronchopneumonia, renal failure with anuria due to tubular degeneration, and severe weakness with or without evidence of paralysis (HSDB, 1994).

Acute fatal exposures of unspecified duration to airborne levels of 300-400 ppm (1,164 - 1,552 mg/m^3) have been reported (HSDB, 1994). A lethal concentration of at least 60,000 ppm (233 g/m^3) MeBr for two hours was reported. Toxic effects preceding death included convulsions, in addition to nausea or vomiting (Wyers, 1945). The lowest lethal level was reported in a child exposed to 257 ppm (1,000 mg/m^3) MeBr for 2 hours; marked exposure-related changes in clotting factors were found after death (HSDB, 1994). The absence of warning qualities, the severity of symptoms, the poor prognosis of the patients, and the variety of CNS effects possible make this compound of particular concern for health effects (Alexeeff and Kilgore, 1983).

During a two-week manufacturing operation, 90 persons were exposed to concentrations of methyl bromide generally less than 35 ppm (136 mg/m^3) (Watrous, 1942). Toxic symptoms developed sometime during the workshift, for example, following a few hours of exposure. In others, the symptoms were delayed and did not develop until several hours following the shift. The symptoms occurred in 33 of the 90 workers and were described as mild systemic symptoms primarily of anorexia, nausea and headache. Anorexia (reported by 25 of the 90 workers) was a common symptom and in some cases lasted for a week or more post-exposure, but without marked weight-loss. In some cases, the symptoms progressed to vomiting. Headache was a fairly common symptom (16 of 90) which disappeared when exposure ceased. While exposure was measured in a crude fashion using a “Frigidaire Leak Detector” (measures halides by color of flame), extensive monitoring was conducted throughout the manufacturing operation. In general, concentrations were at or below the limit of detection of 35 ppm.

A study by Garnier et al (1996) found that two workers similarly exposed to methyl bromide (about 17,000 mg/m3) exhibited substantially different symptoms. Glutathione-s-transferase (GsT) was measured in the erythrocytes of both patients. The patient with severe poisoning possessed GsT and was therefore a conjugator. The second patient who exhibited only mild symptoms lacked measurable GsT activity in the erythrocytes and was therefore classed as a nonconjugator. The genetic polymorphism of GsT is not restricted to the erythrocytes. Conjugators appear to be homozygous or heterozygous bearers of the gene for GsT. As cited by

Garnier et al (1996), the gene is lacking in 20.4 % of whites, 21.8% of African-Americans, 64.6% of Chinese-Americans, 60.2% of Korean-Americans, and 9.7% of Mexican-Americans. Thus, conjugation of methyl bromide with glutathione may be a toxifying step for neurotoxicity and the ability to conjugate may reflect susceptibility to neurotoxicity. Conjugation apparently protects against the cytogenetic effects of methyl bromide (Hallier et al (1993). These latter investigators note that about one-quarter of the human population does not possess GsT activity in erythrocytes, and that this enzyme is not found in erythrocytes of laboratory animals (rats and mice). For this reason, studies in laboratory rodents may underestimate the neurotoxicity of methyl bromide.

Predisposing Conditions for Methyl Bromide Toxicity

Medical: Individuals with psychiatric or neurologic disorders, or those with lung, liver, or kidney disorders may be more sensitive to the toxic effects of methyl bromide (Reprotext, 1993). In addition, a wide variability in response to methyl bromide in the human population is suggested by the studies of Hallier et al (1993) and Garnier et al (1996), due to the impact of the polymorphisms for glutathione-s-transferase in the population. People with high glutathione-s-transferase activity in eruthrocytes may be more sensitive to the neurotoxic effects of methyl bromide due to metabolism to a neurotoxic metabolite than those with low to no levels of this enzyme in the erythrocytes.

Chemical: Methyl bromide exposure may prolong the period of somnolence associated with barbiturates (Honma *et al*., 1985).

V. Acute Toxicity to Laboratory Animals

An LC_{Lo} of 300 ppm (1,167 mg/m³) for 9 hours is reported in guinea pigs (U.S. Public Health Service, 1929). A 30-minute LC_{50} in rats was 2,828 ppm (11,000 mg/m³) (Bakhishev, 1973). An 8-hour LC_{50} in rats was 302 ppm (1,175 mg/m³), with significant decreases in body weight gains noted at concentrations of 125 ppm (486 mg/m³) or higher. Thiopental sleep-time was also increased in rats exposed to 63 ppm (245 mg/m³) or higher (Honma *et al*., 1985). In mice, the LC_{50} is 1,164 ppm (4,700 mg/m³) for 1 hour (Alexeeff *et al*., 1985) and 396 ppm (1,540 mg/m³) for 2 hours (Izmerov *et al*., 1982). Mice exposed to 200 ppm (778 mg/m³) methyl bromide for 6 hours/day, 5 days/week, for 14 days showed a survival rate of 25% (males 1/10, females 4/10) (NTP, 1992).

In five short-term studies, dogs were exposed to methyl bromide for one (233-394 ppm), four (55-283 ppm), 23-24 (25-100 ppm), 30 (10 ppm, then 150 ppm), or 34 (5 ppm) exposure days for 7 hours per day, 5 days per week (Pharmaco LSR, Inc., 1994). One day exposure of 6 dogs to concentrations of methyl bromide between 233 and 394 ppm resulted in CNS effects (tremors, decreased activity, excessive salivation) within 3-7 hours of initiation of exposure. Signs of respiratory effects (labored breathing and gasping) were also observed in 2 dogs. The post-exposure observation period lasted anywhere from 4 to 14 days. However, all dogs appeared to recover from the CNS and pulmonary effects by the second day following exposure.

In the 4 day study, no effects were observed during exposure in the 55 ppm group. Dogs (one of each sex per group) exposed to 156 or 268 ppm methyl bromide showed no effects after one day of exposure. However, all dogs in both groups began exhibiting CNS effects during the second (268 ppm group) or third (156 ppm group) day of exposure. In dogs exposed to 283 ppm, 1 of 3 animals exhibited CNS (excessive salivation and emesis) and pulmonary (labored breathing) effects within 6 hours of exposure on day one. Dogs at the 2 highest concentrations were sacrificed after 2 days of exposure due to severe signs of neurotoxicity, including delirium, thrashing and vocalization, tremors, traumatizing behavior (defined as slamming the head and body into cage walls), depression, ataxia, and irregular gait. Labored breathing was also observed in most of these dogs. Organ weights (brain, kidneys, adrenals, liver, lungs, testes) were not affected and no brain lesions were detected microscopically in animals at any exposure level. The spinal cord and peripheral nerves were not examined microscopically.

In the 30-day exposure study, dogs (4 animals/sex/group) previously exposed to 10 ppm for 24 days without signs of toxicity were exposed to 150 ppm for 6 days. The dogs showed decreased activity starting on the second day of exposure to 150 ppm and were in a poor condition during the final (6th) exposure. The next day, 3 of the 150 ppm males had to be euthanized due to severe neurotoxicity. Histological examinations indicated brain lesions in all treated dogs. In the 23-24 exposure day study, dogs exposed to 103 ppm began exhibiting signs of neurotoxicity (mainly decreased activity) on day 9, but apparently did not progress to more severe CNS effects before the end of the study. No effect was observed at 50 ppm.

VI. Reproductive or Developmental Toxicity

Data on human reproductive or developmental toxicity from methyl bromide exposure are presently unavailable. No maternal toxicity was observed in pregnant rats exposed to methyl bromide up to 70 ppm (272 mg/m^3) from gestation days 1 to 19 (Sikov *et al*., 1981). The only developmental effect was an increase in the incidence of delayed skull ossification of the supraoccipital plate. The NOAEL was 20 ppm methyl bromide for developmental effects.

Rats exposed to methyl bromide up to 90 ppm 5 days per week at premating and during gestation showed decreased fertility in the dams (American Biogenics Corp., 1986). Pups born to these dams showed decreased body weights postnatally. Since the pups were not directly exposed to methyl bromide until after weaning, the decreased body weight may be due to in utero exposure. The NOAEL for these effects was 3 ppm.

In an abbreviated developmental toxicity study, pregnant rabbits exposed to 70 ppm starting on gestation day 1 showed severe neurotoxicity and mortality after 1 week of exposure (Sikov *et al*., 1981). Exposure of the rabbits was stopped after gestation day 15 (Hardin *et al*., 1981). No developmental effects were observed in the fetuses of the one survivor. A NOAEL for developmental toxicity cannot be determined from this study since it was terminated prematurely. The NOAEL for maternal toxicity was 20 ppm.

In two subsequent studies, pregnant New Zealand white rabbits exposed to methyl bromide at 80 ppm from gestation days 7 to 19 showed neurotoxicity and decreased body weight (Breslin *et al*., 1990). Developmental effects observed in the fetuses of the 80 ppm group included gall bladder agenesis, fused sternebrae, and decreased fetal body weight. No effects on the fetuses and does were observed at 40 ppm (155 mg/m^3).

After consideration of the above studies showing developmental effects in rabbits and rats, the California Department of Pesticide Regulation concluded that these effects were significant and warranted regulation on the use of methyl bromide to decrease human exposure. However, the California Developmental and Reproductive Toxicity (DART) Committee for Proposition 65 concluded the animal evidence insufficient in meeting the listing standard of "clearly shown to cause developmental or reproductive toxicity" for the purposes of Proposition 65.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 1 ppm (3,900 μg/m^3)

Study	Watrous, 1942
Study population	humans, 90 workers
Exposure method	acute inhalation of 35 ppm
Critical effects	anorexia, nausea, headache
LOAEL	35 ppm
NOAEL	not available
Exposure duration	2 hours
Extrapolated 1 hour concentration	59 ppm $C^{1.33}$ (2 hr) = $C^{1.33}$ (1 hr)
LOAEL uncertainty factor	6
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	60
Reference Exposure Level	1 ppm (3.9 mg/m^3; 3,900 μg/m^3)

The evaluation by Watrous (1942) of 90 workers indicated that symptoms developed during the workshift. We thus assumed a 2 hour exposure was sufficient to cause the symptoms to occur. Using the value for the exponent "n" in the modified Haber's Law equation $C^n \times T = K$ of 1.33, derived by Zwart et al. (1992) from the data of Irish et al. (1940), we extrapolated to a one-hour LOAEL of 59 ppm. Applying an uncertainty factor of 6 for extrapolation of a LOAEL to a NOAEL for mild adverse effects, and an additional uncertainty factor of 10 for intraindividual variability yields an acute REL of 1 ppm.

Level Protective Against Severe Adverse Effects

CNS and pulmonary effects were observed within 7 hours in dogs exposed individually to concentrations of methyl bromide between 233 and 394 ppm. Signs of toxicity included tremors, decreased activity, excessive salivation, labored breathing, and gasping. In the 4-day study (exposed 7 hours/day), 1 of 3 dogs exposed to 283 ppm exhibited similar signs of CNS and pulmonary toxicity on the first day of exposure. Dogs (2 per group) exposed to 156 and 268 ppm showed signs of neurotoxicity during the second or third day of exposure. Lacrimation was observed after 5 hours exposure to 156 ppm in one dog, and lacrimation combined with labored breathing, prostration, and decreased activity was observed in both dogs on days 3 and 4. At 233 ppm, trembling extremities, panting, rapid eye blink, and tremors were observed after 5 hours. Dogs exposed to 103 ppm exhibited no adverse effects after a single exposure, and less severe signs of neurotoxicity on day 9. A 7-hour (1 day) exposure to 103 ppm was therefore chosen as the NOAEL for this study. Applying the value of 1.33 for the exponent "n" in the modified Haber's equation yields a one-hour concentration of 445 ppm. Dividing by a cumulative uncertainty factor of 100 (10 for interspecies and 10 for intraindividual variability) yields a level protective against severe adverse effects of 4.45 ppm.

Level Protective Against Life-threatening Effects

Dogs exposed individually to concentrations of methyl bromide between 233 and 394 ppm (233, 314, 345, 350, or 394 ppm) did not show signs of CNS or pulmonary toxicity by day 2 of the post-exposure observation period (Pharmaco LSR, Inc., 1994). However, the observation period was inconsistent from animal to animal, lasting from 4 to 14 days. In the 4-day study, 1 of 3 dogs was "humanely sacrificed" following one 7-hour exposure to 283 ppm methyl bromide due to "extreme clinical (CNS and pulmonary) signs." These signs included delirium, thrashing and vocalization, tremors, traumatizing behavior (defined as slamming the head and body into cage walls), depression, ataxia, and irregular gait, rales, and a cachectic appearance. After the second day of exposure, all the dogs in the 268 ppm group and the other 2 dogs in the 283 ppm group were sacrificed due to extreme clinical signs. Dogs exposed to 156 ppm for 4 days had irregular gait, decreased activity, and labored breathing. However, the post-exposure observation time before necropsy was unspecified. Based on these results, the highest nonlethal level observed in dogs was 268 ppm for a 7-hour exposure. Dogs exposed for longer durations at this level or exposed to higher concentrations were humanely sacrificed due to severe CNS and pulmonary toxicity. The CNS toxicity was severe enough to be considered life-threatening.

A comparison of the toxicity data for mice and dogs suggests that dogs are more sensitive to methyl bromide, even though the dogs were humanely sacrificed before they actually died from exposure. The CNS and pulmonary effects at concentrations higher than the NOAEL (268 ppm) were severe enough in the dogs to be considered life-threatening effects. Extrapolation to a one-hour concentration using modified Haber's Law and an exponent of 1.33, yields a one-hour concentration of 1157 ppm. Using an uncertainty factor of 100 for interspecies and intraspecies extrapolation, the level protective against life-threatening effects is 115 ppm (447 mg/m^3).

Comparison with studies in mice

By using data from an LC_{50} study in Swiss-Webster mice (Alexeeff *et al*., 1985), a benchmark concentration could be determined for 1-hour exposure to MeBr. Exposure concentrations ranged from 870 to 5,929 mg/m³ (224 to 1,524 ppm) and clinical signs of toxicity were observed for up to 7 days following exposure. Dose-dependent mortality was observed at the 4 highest concentrations (1/6, 4/6, 5/6, and 5/6 deaths, respectively for the 3,824, 4,696, 5,770, and 5,929 mg/m³ groups). A log-normal probit analysis (Crump, 1983) of the 1-hour mouse lethality data was employed to determine a benchmark concentration. The maximum likelihood estimate (MLE) associated with a 5% incidence of lethality was 896 ppm. The 95% lower confidence limit (LCL) on the concentration resulting in 5% lethality (BC_{05}) was 747 ppm (2,906 mg/m³). An uncertainty factor of 3 to account for interspecies variability since the BC_{05} accounts for some degree of variability and an additional uncertainty factor of 10 to account for individual variation among people were applied to the LCL of the BC_{05}.

$$\text{level protective against life-threatening effects} = BC_{05}/(UF)$$

The total uncertainty factor was 30. The final level for MeBr based on mice was therefore 747 ppm/30 = 25 ppm (97 mg/m³). However, since dogs are the most sensitive species, we recommend using the value of 2.7 ppm as the level protective against life-threatening effects. The MLE and 95% lower confidence limits (LCL) for the 1% and 5% response rates are compared below.

Response rate	MLE (ppm)	95% LCL (ppm)	Level (ppm)
5%	896	747	25
1%	790	618	21

VIII. References

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